



## Il ruolo delle aziende nella ricerca

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*Milano, 9 dicembre 2009*

# Presentazione

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- Chi è Novartis: focus sulla Ricerca Clinica
- Strategie di sviluppo nuove molecole in ambito oncologico
  - Approccio multidisciplinare:
    - Medicina traslazionale
    - Ruolo dei biomarkers
    - Terapia individualizzata
    - Aspetti farmacoeconomici
- Panoramica Molecole in sviluppo

# Chi è Novartis

*Dati 2008*

- Novartis è azienda leader, a livello globale, nell'area della Salute
  - **Fatturato** 41,5 miliardi di dollari
  - **Investimenti R&S** 7,2 miliardi di dollari
  - **Dipendenti** 96.700



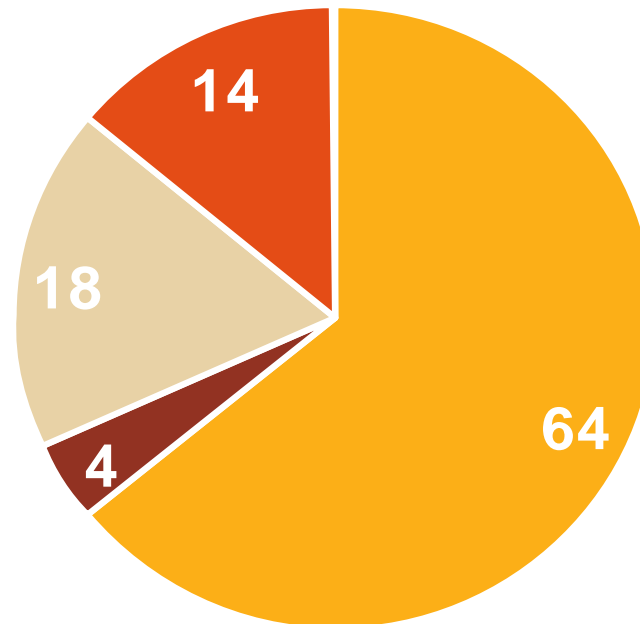
Il Gruppo Novartis è presente in oltre 140 Paesi

# Profilo di un protagonista

## *Le quattro divisioni*

L'unico grande Gruppo attivo in tutti i settori della Salute

- Farmaceutici
- Vaccini e Diagnostici
- Sandoz (farmaci generici)
- Consumer Health (OTC, Ciba Vision, Animal Health)



*(% su fatturato globale-dati 2008)*

# Novartis in Italia

## Numeri e presenza del Gruppo nel nostro Paese

Tra i leader del mercato nazionale in tutte le aree di attività

- **Fatturato 2008**  
1.444 milioni euro
- **Investimenti in Ricerca & Produzione**  
192 milioni di euro
- **Investimenti in Ricerca & Sviluppo**  
134 milioni di euro
- **Collaboratori**  
3800, di cui oltre 1.200 in produzione e più di 500 in R&S



# Ricerca clinica Farma, un impegno costante e crescente

## 2008, sperimentazioni e risorse dedicate

- 37 milioni di euro (+ 13% rispetto al 2007)
- 134 studi
- 7.805 pazienti

Area	Ricerche	Centri	Pazienti
Oncologia ed ematologia	70	211	4.303
Cardiovascolare e metabolismo	24	174	1.397
Immunologia/Infettivologia	15	24	1.265
Respiratorio	10	42	162
Metabolismo osseo/Infiammatorio	7	15	92
Neuroscienze	5	62	531
Oftalmologia	3	8	55
<b>Totale</b>	<b>134</b>	<b>536</b>	<b>7.805</b>

# Ricerca Farmaceutica

## *I primati di Novartis Italia nella ricerca clinica*

- Al primo posto tra le aziende farmaceutiche nel nostro Paese
- Al vertice del Gruppo internazionale

### Sperimentazioni cliniche promosse in Italia

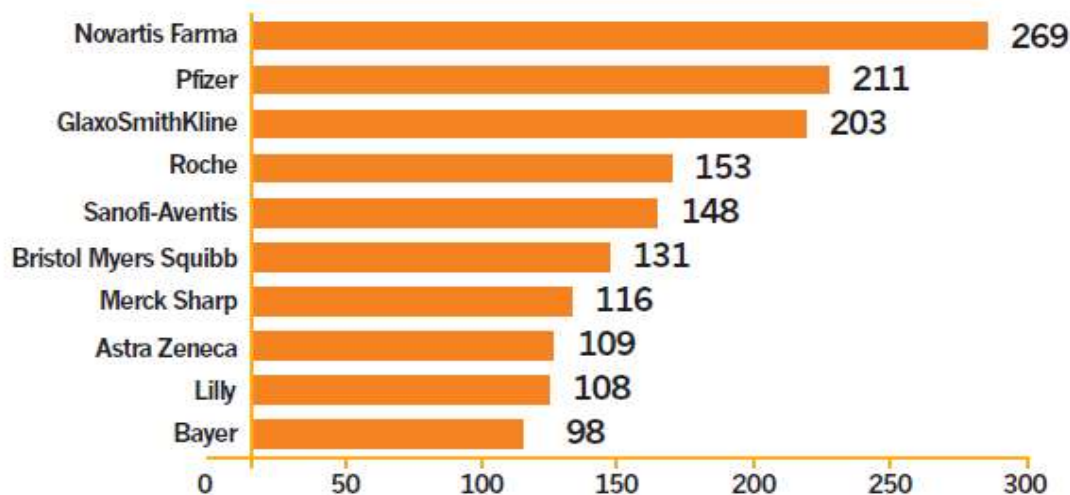


Grafico tratto dal VII Rapporto dell'Osservatorio Nazionale sulla Sperimentazione clinica dell'Agenzia Italiana del Farmaco (dati dal 1.01.2000 al 31.12.2007)

# NIBR - Novartis Institute for Biomedical Research

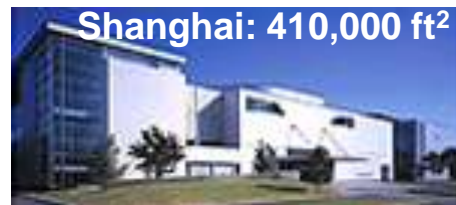
## *I centri di ricerca*

- NIBR ha il quartier generale a Cambridge Massachusetts USA e una sede a Basilea.
- Altri centri collegati sono a Horsham, Gran Bretagna; Vienna, Austria; Tsukuba, Giappone; East Hanover, New Jersey, USA; Emeryville, California, USA; e Shanghai, Cina.
- La ricerca nell'area oncologia viene fatta a Cambridge e a Basilea.



# Novartis Oncology – una visione globale: un leader mondiale nella ricerca e sviluppo di farmaci oncologici

## Sviluppiamo farmaci per proteggere e migliorare la salute e la qualità della vita dei pazienti affetti da tumore



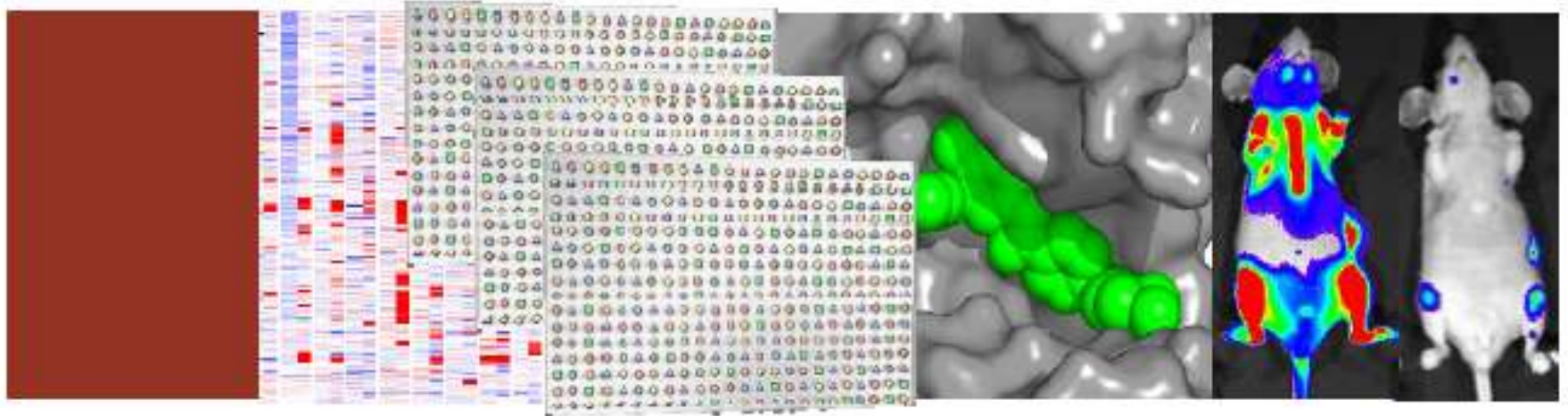
A breve

- La Business Unit è stata creata nel 2000 concentrandosi su Oncologia e Ematologia
- Occupa 5.215 collaboratori in tutto il mondo che lavorano in squadra
- All'interno del NIBR 370 ricercatori sono dedicati alla Ricerca Oncologica
- Maggiori siti di R&S: Florham Park (US), Basilea (CH), Cambridge (US), Emeryville (US), e a breve Shanghai
- Elemento chiave per la crescita di Novartis Farma

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The application of biomarkers to cancer drug discovery and development

# Biomarkers: working definitions

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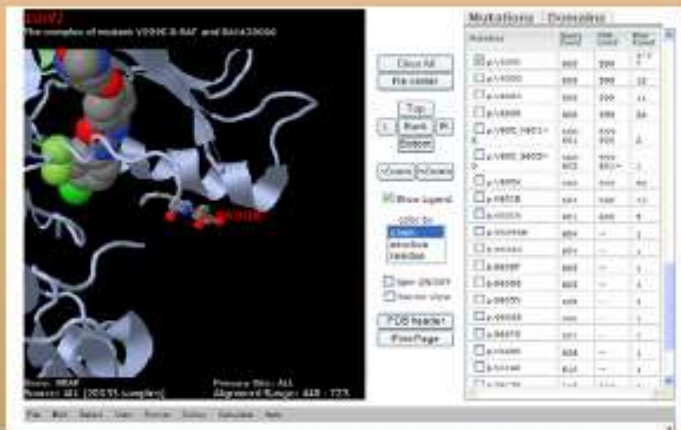
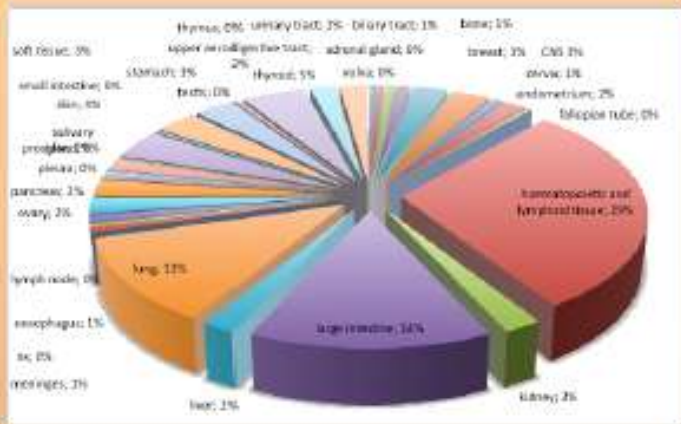
<b>Biomarker type</b>	<b>Working Definition</b>
Pharmacodynamic	Used to measure the activity of a drug target and relate drug exposure to drug action.
Cellular response	Used to measure the resulting effect of target inhibition on cellular properties (e.g. proliferation, apoptosis, glucose uptake)
Tumor response	Used to measure reduction in tumor burden (e.g. CT scans, CEA, LDH, CA125, BCR-ABL allele)
Predictive	Used to select patients for a specific therapy (e.g. ER+ breast cancer and tamoxifen or Femara)
Safety	Used to monitor the host for on and off-target toxicologic effects of given therapeutics (e.g. QTc, AST, ALT)

## Overview: Biomarkers and drug discovery

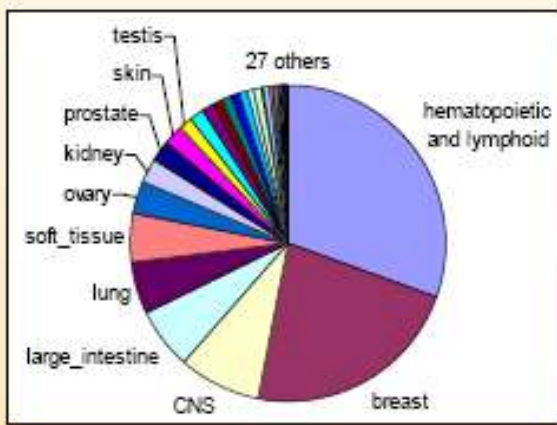
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- **Our goal** is to have a set of pharmacodynamic, cellular response, and patient selection biomarkers for each discovery program.
  - The development of the majority of these biomarkers is based on underlying project-related biology.
- **New Infrastructure:** we are developing new capabilities that enable the discovery and validation of project relevant biomarkers.
  - Databases:
    - OncExpress: a large-scale cancer expression database (ca. 30,000)
    - OncBase: a large-scale gene mutation database.
    - OncCNV: a large-scale cancer copy number database
  - The Cell Line Encyclopedia
  - The Primary Human Tumor Collection
  - shRNA platform and pooled screening
- **The IAP Program:** approaches to biomarkers will be illustrated in the context of the IAP program.

**Onc\*Base:** a database containing gene mutation data from public domain and internal sources. Allows rapid queries of genetic epidemiology from >260,000 tumors.



**OncExpress:** a database containing gene expression profiles and curated sample meta-data from >500 data sets



Tissue type	No.
normal	4044
benign	578
primary tumor	23398
metastatic	3627
other	2823
total	34250

**OncCNA:** a database containing high-density SNP array data from cancer samples allowing for the cataloging of deletions, amplifications and LOH events.





### Goals and progress

- To systematically collect, characterize and experimentally profile 1000 cancer cell lines.
- Derived from Worldwide commercial and some academic sources
- 630 cell lines completed, >700 acquired.
- Large-scale cmpd profiling at GNF and in NIBR.

### Genomic Profiling of all cell lines

Gene Copy Number data – Affymetrix SNP 6.0 array

552 samples completed.

Gene Expression - U133 plus 2.0 array

501 samples completed.

Mutation Profiling - OncoMapver3.0 (iPlex)

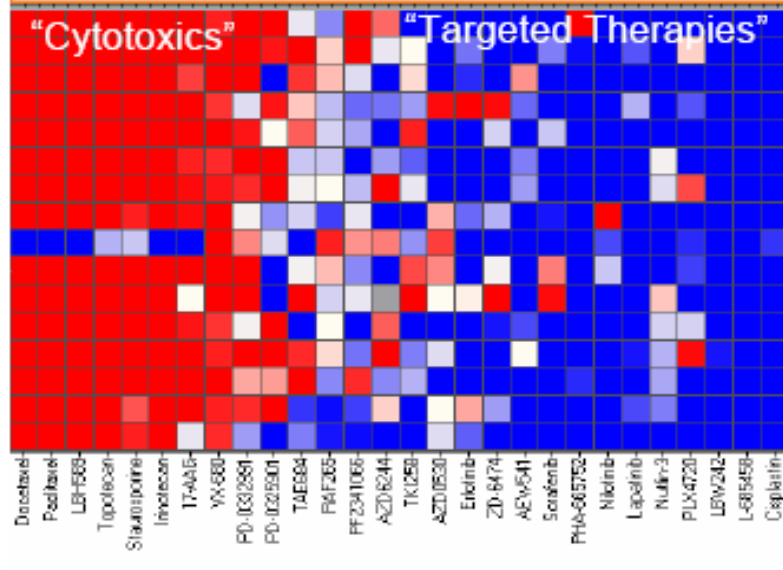
570 samples completed

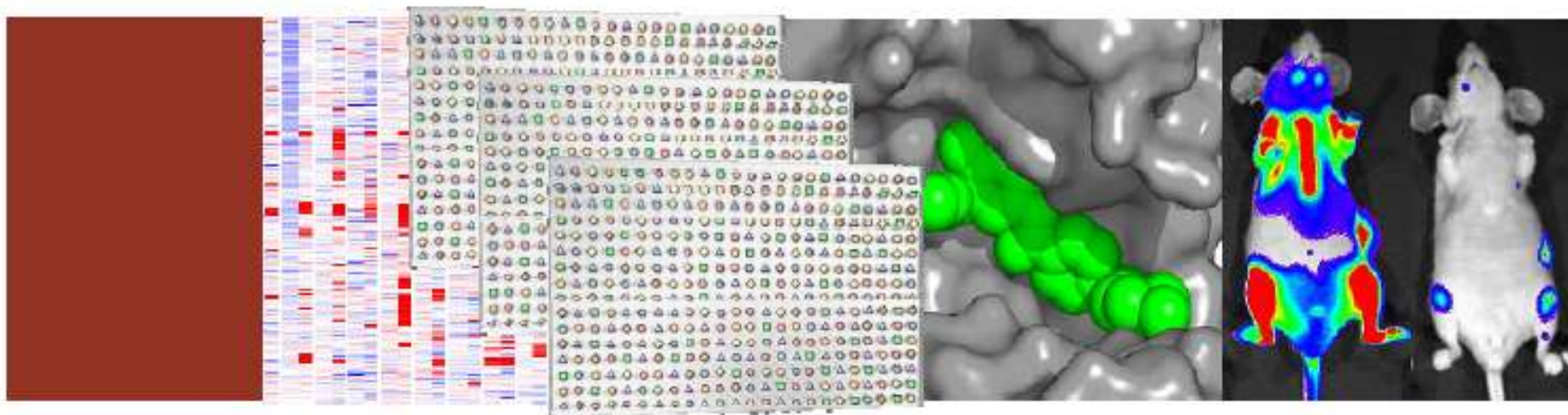
Exon Sequencing

(Hybrid capture/Illumina using 1400-gene bait)

Pilot ongoing; planned start Q3 2009

### GNP Pilot Cmpd Profiling Experiment

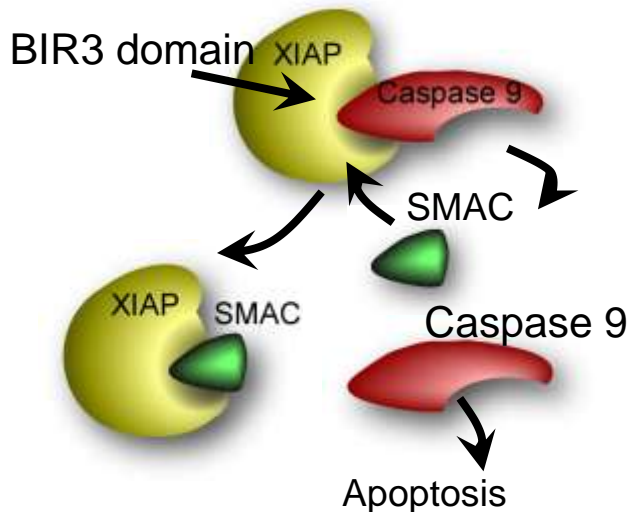




## Targeting the inhibitors of apoptosis (IAPs)

*...and the discovery of pharmacodynamic and patient stratification biomarkers.*

# IAP Program - Background and scientific rationale



- The BIR3 domain of IAPs binds and represses Caspases and prevents apoptosis
- When released from mitochondria, the SMAC peptide binds the IAPs (e.g. XIAP), alleviating Caspase 9 repression and activates apoptosis
- Defects in apoptosis proteins including the IAPs permit cancer growth, metastasis, and resistance to chemotherapy
- LCL161 mimics the active part of the SMAC peptide, inhibiting (and degrading) IAPs, releasing caspase 9 and activating apoptosis
- By degrading cIAP1, LCL161 also shunts tumor NFkB signaling towards apoptosis if TNF- $\alpha$  is present

# Development of LCL161

First-in human study with LCL161 ongoing

Key development indications based on LCL161-taxane synergy:

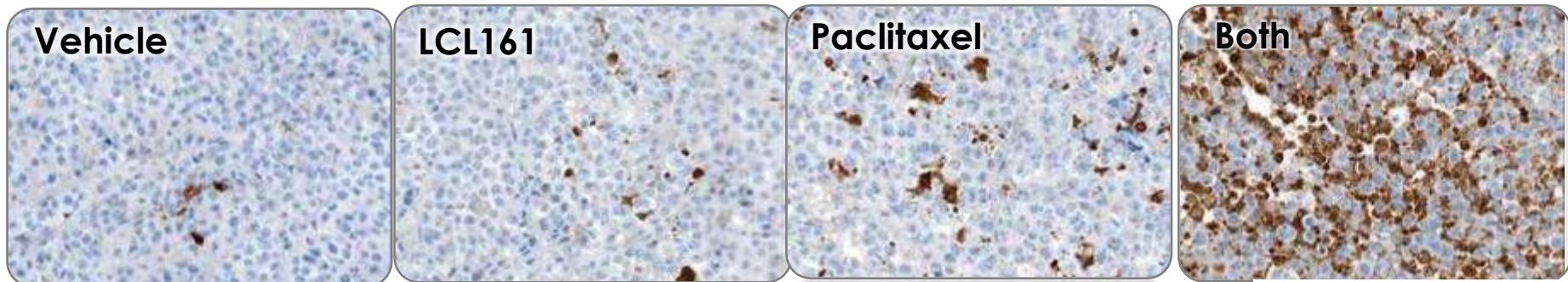
## Breast cancer and melanoma

- LCL161 in combination with weekly paclitaxel

## NSCLC and ovarian Cancer

- LCL161 in combination with q3 week carboplatin and paclitaxel

On-going effort to explore indications that have elevated TNF $\alpha$  for a single agent trial



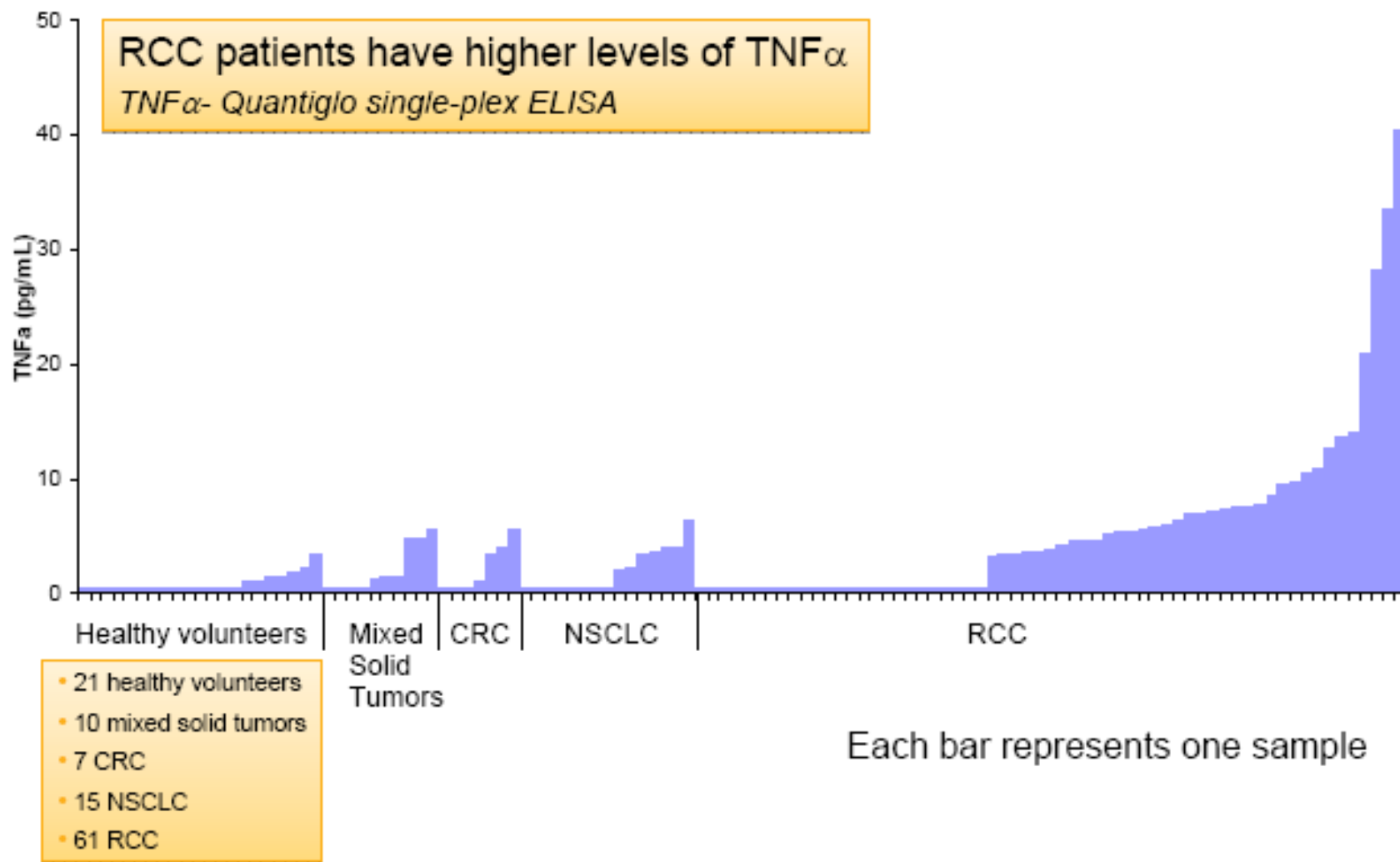
Caspase 3 Staining in Melanoma A2058 model

# The IAP Program



Biomarker plan for the current clinic trials

From the bench to the bedside



# As the Oncology Environment Evolves...

*We continue to advance and adapt our R&D strategies to drive the next generation of cancer therapeutics*



## Research & Discovery

- Deliver mechanism based therapeutics



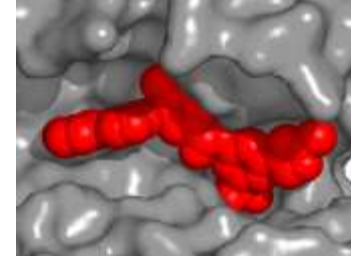
## Translational Medicine

- Redefine the disease; identify right patient population



## Molecular Diagnostics

- Provide tools to enable individualized therapy



## Life Cycle Management

- Broad development programs, while focusing on next generation products



## Partnering

- Acquire high-quality compounds to augment pipeline

# Ensuring that We Can Redefine the Disease and Identify the Right Patients for our Medicines Is Key to Success

***We are building out...***

***Expanded TM Organization***

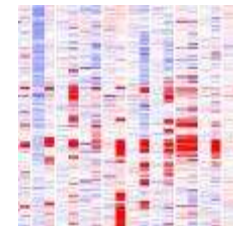
***to drive TM strategy & provide optimal support for projects***



***Novel assays for biomarkers and minimally invasive technologies (CTC, PET imaging)***



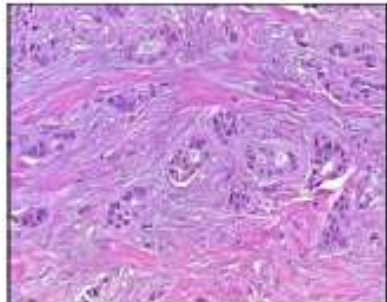
***Interrogation of archival tissue to correlate clinical outcomes with molecular signature of tumors***



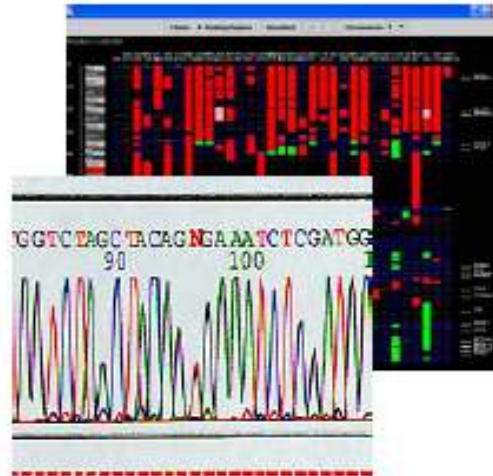
***Patient stratification as an integral part of all early clinical programs***

TM = Translational Medicine

# Oncology Translational Medicine



Histology



Genetics



BRAF mutation  
and Melanoma



People  
and Families



# BEST-Rx approach requires coordination across projects, sites and laboratory

Sites



Define molecular subtype of tumor

Patient

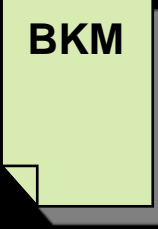
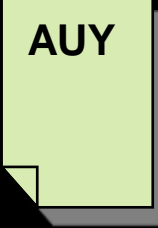
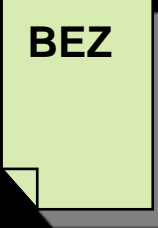
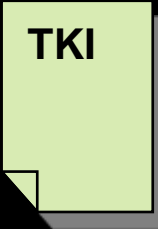


Central Analysis



Patient's Tumor Results

Trials



Treat with Rx most likely to benefit the patient

FGFR

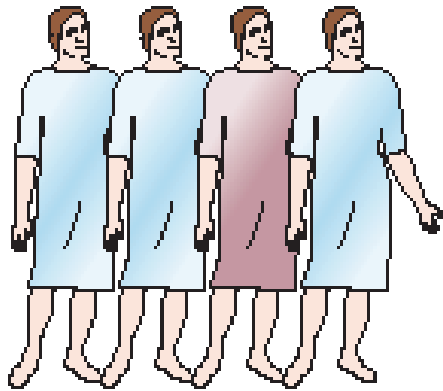
PIK3CA

HER2+

PIK3CA

# Move to personalised medicine

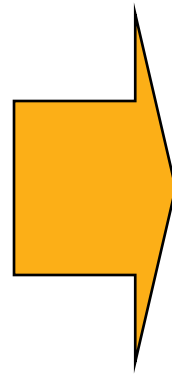
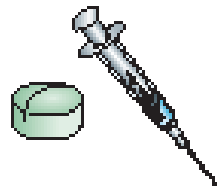
## a Current therapy



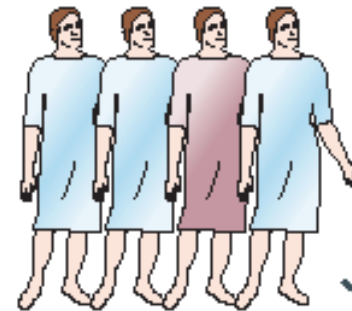
All patients with cancers of a certain tissue type (for example, pancreatic cancer)

+

One drug or limited drug combination



## b Future therapy



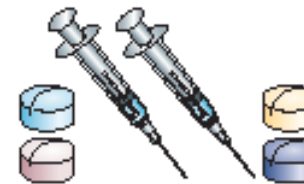
Pool of cancer patients

Genetic screen



Patient A

+



Pool of agents specific for genetic alterations

Personalized drug cocktail



From Lengauer et al., Nat Rev Drug Discov., 2005

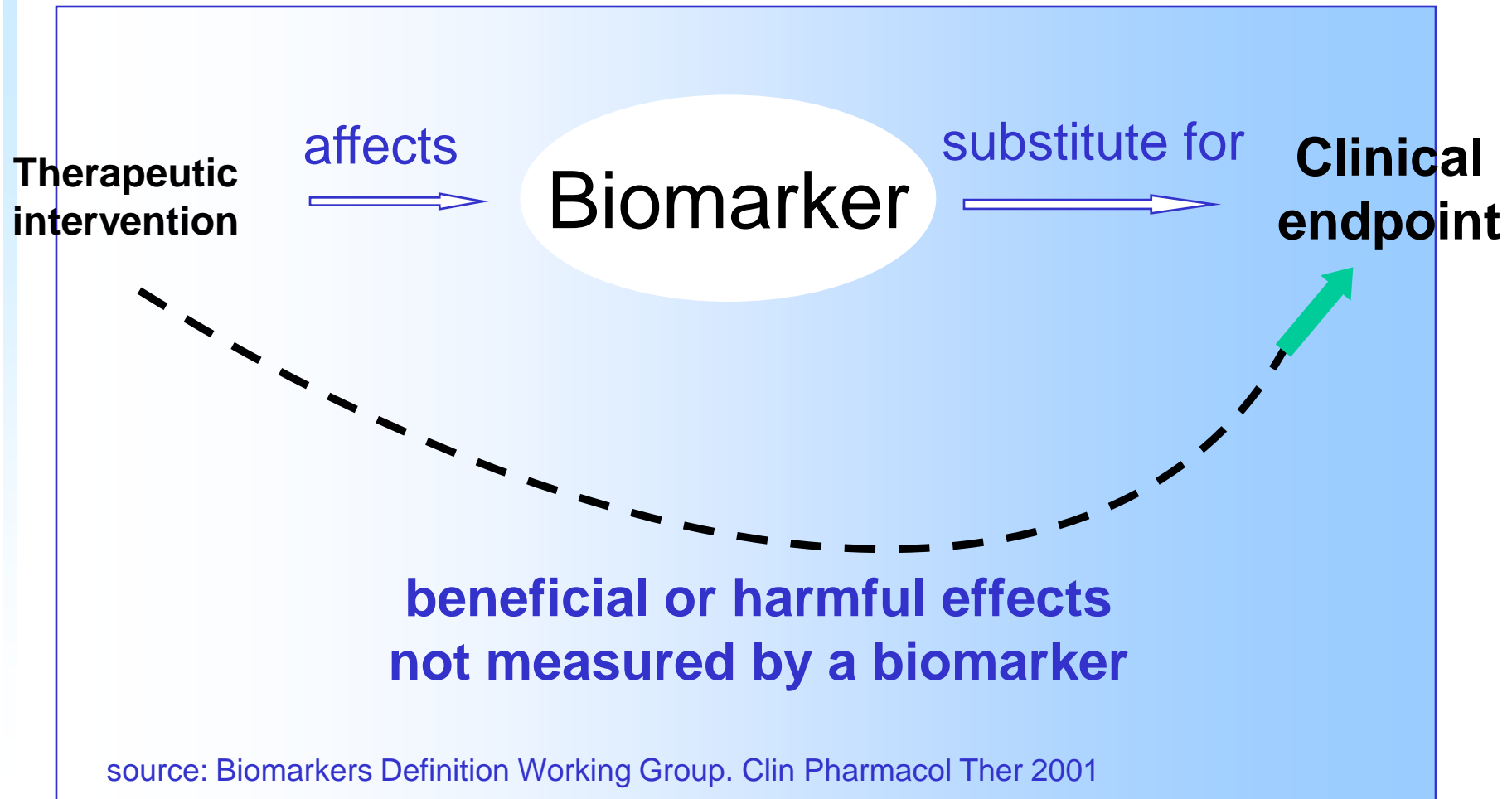
# Vantaggi attesi per l'approccio multidisciplinare seguito in Novartis Oncology

- Identificazione su base genetica e molecolare delle sottopopolazioni sensibili ai farmaci
- Identificazione di biomarkers per
  - monitorare:
    - Farmacodinamica
    - Risposta clinica
    - Sicurezza d'impiego
  - Identificare fattori predittivi della risposta
- Vantaggi per la spesa sanitaria

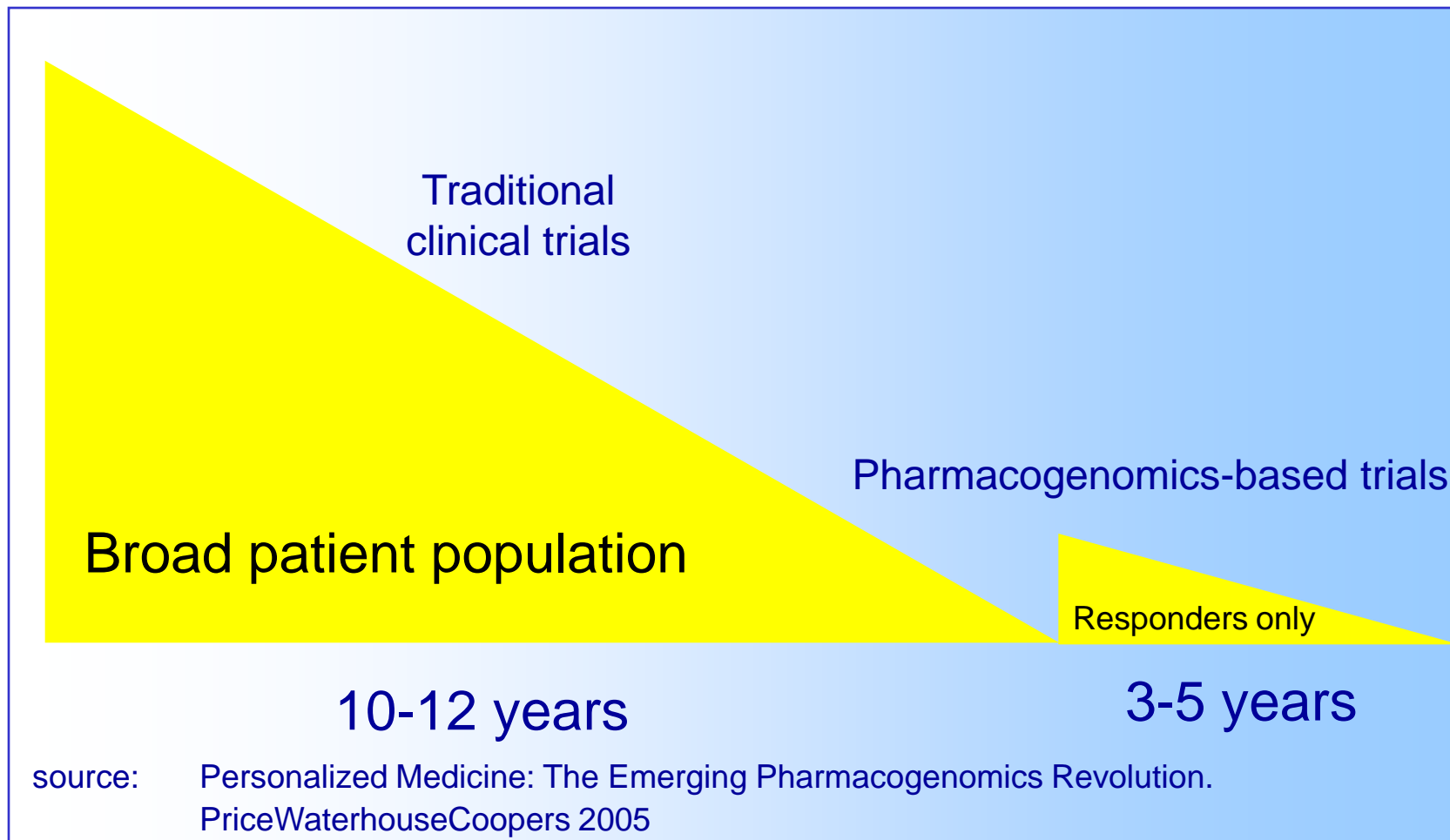
# Personalised medicine

- Stratification of patients according to their response to a particular medication in terms of:
  - Good response to the therapy (efficacy)
  - Risk of ADRs (safety)
- Stratification of diseases into specific subtypes

# Effects of therapeutic interventions on biomarkers and clinical endpoints



# Pharmacogenomics might streamline clinical trials



# Possible advantages of personalised medicines

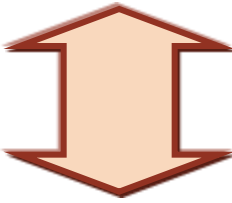
- Improving patient safety
- Increasing effectiveness
- Increasing economic efficiency
- Enhancing patient access
- Improving health outcome

Source: US DHHS. Realizing the Promise of Pharmacogenomics:  
Opportunities and Challenges. June 2007

# Drug Discovery and Innovation: The Core Dilemma

## A. PHARMA INDUSTRY

- 1. Higher R&D Costs
- 2. Smaller Return on Investments
- 3. Falling R&D Productivity



**Discover, develop and make accessible effective therapies for cancer !**

## B. HEALTH AUTHORITIES

- 1. Increasing/ Higher costs of drugs
- 2. Higher epidemiology in many cancer types



## C. PHYSICIANS

- 1. Need for more effective use of treatments
- 2. Need of high caliber Scientific Projects



## D. PATIENTS (ASSOCIATIONS)

- 1. High need of effective and safe treatments available in the market



**They all have a common goal !**

## B. Closer collaboration with Health Authorities and Regulatory bodies

### PHARMA INDUSTRY

- ❑ **Select compounds in early phases**
- ❑ **Reduce internal beaurocracy/ processes burden**
- ❑ **Adopt a more flexible approach in price negotiations**



### HEALTH AUTHORITIES

- ❑ To share a preliminary **Health Technology assessment in every phase of the drug development process** in order to better target the diseases and find a favorable cost/benefit ratio
- ❑ To **reduce beaurocracy for clinical trials, including Phase I**
  - Focus on simplified GCP (Good Clinical Practices)
  - Centers of reference
- ❑ To move drug more rapidly into clinical practice **applying wider conditional approvals**
- ❑ To apply **more flexible price/reimbursement schemes**

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- **Panoramica Molecole in sviluppo**

# Pipeline: an Impressive Portfolio of Targeted Therapies – 5 Innovative Compounds in Registration Trials

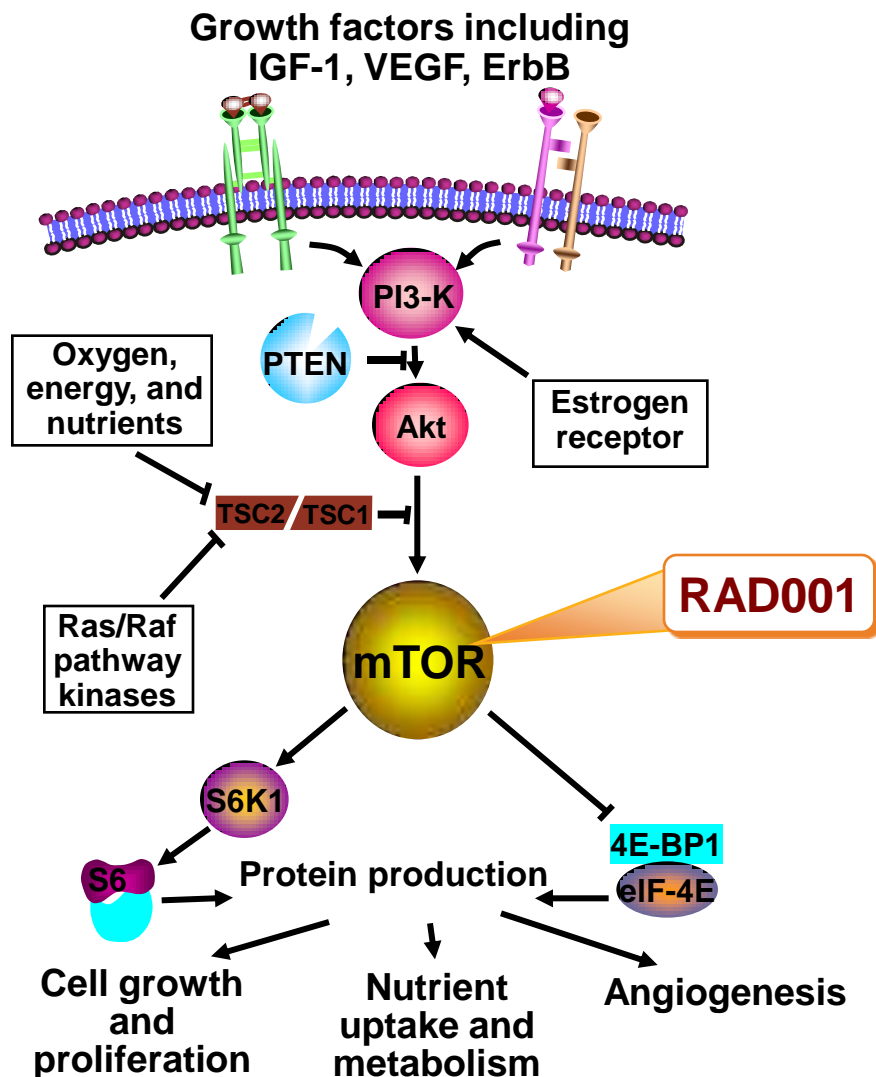
Exploratory		Confirmatory		Registration
		Ph I/II	Ph III	
HCD122 CD-40	BKM120 PI3K	PKC412 ASM <sup>2</sup> ✓	EPO906 Ovarian cancer ✓	Afinitor RCC <sup>3</sup>
TKI258 VEGFR/PDGFR/FGFR	LCL161 IAP	LBH589 Hodgkin's lymphoma ✓	SOM230 Cushing's disease ✓	
RAF265 B-RAF/VEGFR	MCS110 CSF-1	LBH589 Hemat. & solid tumors	ASA404 NSCLC <sup>7</sup> ✓	
BEZ235 PI3K/mTOR	BQS481 Eg5	RAD001 Solid tumors	PKC412 AML <sup>1</sup>	
AUY922 HSP90	HSP990 HSP90	EPO906 Solid tumors	RAD001 NET <sup>6</sup>	
BHQ880 DKK-1	LDE225 Smoothened	Exjade <sup>®</sup> Hered. hemochromatosis	Tasigna <sup>®</sup> GIST <sup>8</sup> / newly diagnosed CML <sup>4</sup>	
BGT226 PI3K, mTOR			SOM230 Aeromegaly/Carotoid	
			Zometa <sup>®</sup> Adjuvant breast cancer	

- NME
- LCM
- ✓ NME Pivotal trial

<sup>1</sup> Acute myeloid leukemia    <sup>2</sup> Aggressive systemic mastocytosis    <sup>3</sup> Gastrointestinal stromal tumor    <sup>4</sup> Chronic myeloid leukemia  
<sup>5</sup> Renal cell carcinoma    <sup>6</sup> Neuroendocrine tumor    <sup>7</sup> Non small cell lung cancer    <sup>8</sup> Cutaneous T-cell lymphoma  
<sup>9</sup> Gilvec is also being developed by the Respiratory franchise for pulmonary arterial hypertension

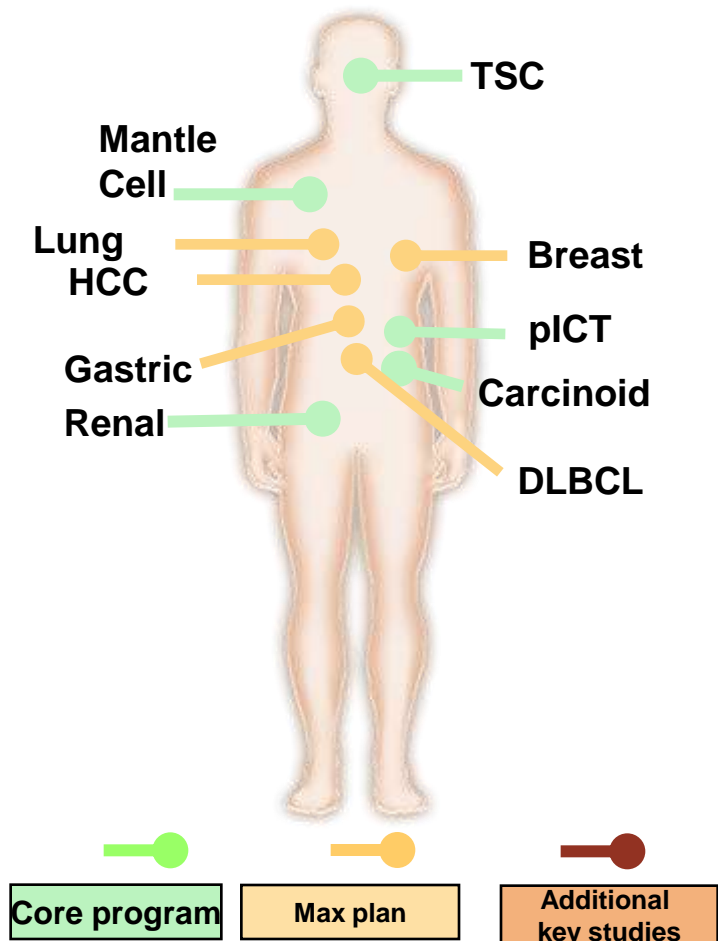
9 | NORD 2009 | David Epstein | Novartis OBU

# RAD001- Targeting the PI3K/AKT/mTOR Pathway



- RAD001 (everolimus) is novel, oral inhibitor of the ser/thr kinase, mTOR
- mTOR is a central regulator of multiple signaling pathways involved in cancer
- Blocking mTOR leads to inhibition of cellular growth/proliferation, cellular metabolism and angiogenesis

# RAD001 Clinical Development Program



Tumor	Ph	Status
RCC 2 <sup>nd</sup> /3 <sup>rd</sup>	Ph 3	Approved
Carcinoid	Ph 3	Enrolled
pICT 1 <sup>st</sup> line	Ph 3	Enrolling
RCC 1 <sup>st</sup> line	Ph 2	Enrolling
Mantle Cell	Ph 2	Enrolling
TSC AML	Ph 3	Enrolling
TSC SEGA	Ph 3	Enrolling
Gastric 2 <sup>nd</sup> /3 <sup>rd</sup>	Ph 3	Jun 2009 FPFV
Breast ER+	Ph 3	Jun 2009 FPFV
HCC	Ph 3	Oct 2009 FPFV
Breast Her2+	Ph 3	Jun 2009 FPFV
Breast Her2+	Ph 3	Jun 2009 FPFV
DLBCL	Ph 3	May 2009 FPFV
NET w SOM	Ph 3	Oct 2009 FPFV
Adjuvant RCC	Ph 3	1Q 2010 FPFV
RCC 1st vs IFN	Ph 3	May 2009 FPFV
RCC 1st Sutent	Ph 2	Jul 2009 FPFV

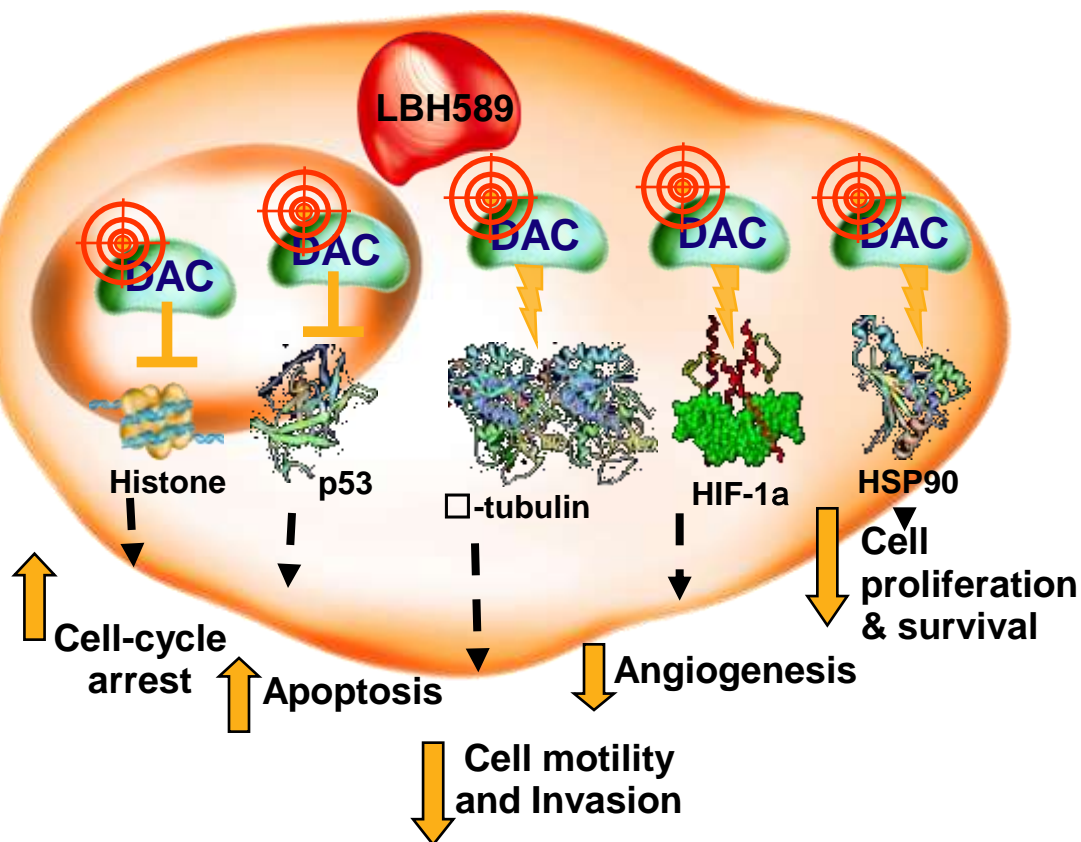
\* assuming priority review

# Everolimus (RAD001): Oral mTOR Inhibitor

## Phase III Trials in Multiple Cancers

Tumor (Study Code)	Phase	Status
Carcinoid (RADIANT-2)	3	Enrolled
pICT 1 <sup>st</sup> line (RADIANT-3)	3	Enrolled
RCC 1 <sup>st</sup> line (RECORD-2)	2	Enrolling
Mantle Cell (PILLAR-1)	2	Enrolling
Tuberous Sclerosis Complex AML (EXIST)	3	Enrolling
Tuberous Sclerosis Complex SEGA (EXIST)	3	Enrolling
Gastric 2 <sup>nd</sup> /3 <sup>rd</sup> line (GRANITE)	3	Starting soon
Breast ER+ (BOLERO-2)	3	Starting soon
Breast HER2+ (BOLERO-1)	3	Starting soon
Breast HER2+ 2 <sup>nd</sup> /3 <sup>rd</sup> (BOLERO-3)	3	Starting soon
DLBCL (PILLAR-2)	3	Starting soon
HCC (EVOLVE)	3	Planned

# Panobinostat (LBH589): a Multi-Targeted Deacetylase (DAC) Inhibitor



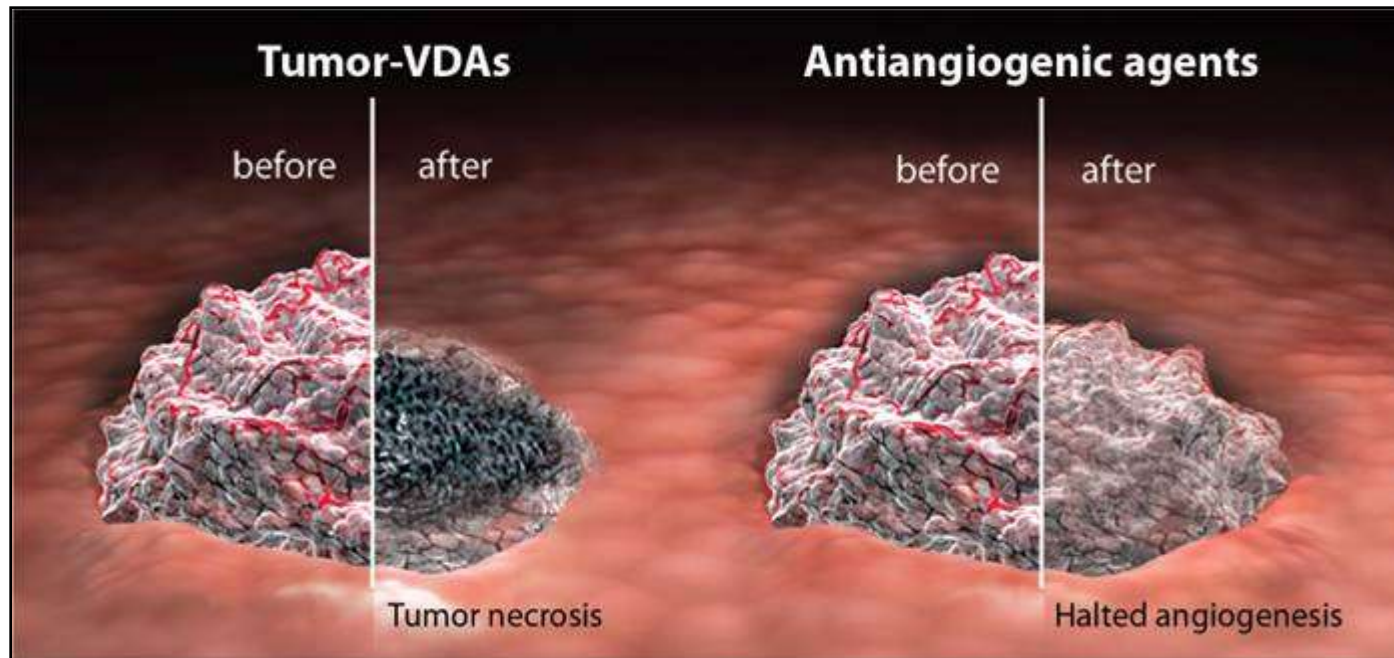
Prince HM et al. Presented at ASCO 2007. Abstract # 3500;  
Spencer A et al. Presented at ASH 2007. Abstract # 907; Sharma S  
et al. Presented at ECCO 2007. Abstract # 702; Novartis data on file

- Panobinostat displays superior nanomolar potency in the inhibition of Class I, II, and IV HDAC enzymes compared with other HDAC inhibitors
- Through pan-DAC inhibition, panobinostat interferes with multiple pathways implicated in cancer
- Oral and i.v. formulations are being developed to increase flexibility in treatment approach

# Panobinostat (LBH589): Clinical Development Program

Core Program		
<b>HL third-line post-ASCT and Gem/Vin/Vinb Tx</b> 400 mg LBH589 3 x weekly; 21 day cycle	Phase II	Planned
<b>MM (relapsed/refractory)</b> Dose escalation with lenalidomide and dexamethasone, safety expansion	Phase I/II	Ongoing
<b>CTCL <math>\geq 2</math> prior Tx</b> LBH589 20 mg d1, 3, 5 x qw; q28 day cycle with/without prior bexarotene	Phase II	Ongoing
Rel / Ref AML + HR MDS	Phase I/II	Ongoing
Second-line BC SA trastuzumab	Phase I/II	Ongoing
HRPC SA doc + prednisone	Phase I/II	Ongoing
Exploratory		
NSCLC / SCLC / mesothelioma	Phase I/II	Ongoing
Various GI Cancers	Phase I/II	Ongoing
Other solid tumors	Phase I/II	Ongoing
Advanced heme tumors	Phase I/II	Ongoing

# Tumor-VDAs vs Antiangiogenic Agents



- Disrupts established blood vessel endothelial lining
- Causes vessel occlusion and necrosis
- Major effect on central part of tumor
- Interferes with new blood vessels
- Inhibits endothelial proliferation and migration
- Major effect on peripheral part of tumor

Tozer et al. *Nat Rev Cancer*. 2005;5:423-435.

Patterson and Rustin. *Clin Oncol (R Coll Radiol)*. 2007;19:443-456.

Baguley. *Lancet Oncol*. 2003;4:141-148.

# ASA404 Clinical Program

## NSCLC

- **ATTRACT-1** First-line, stage IIIb/IV, all histologies,
  - ASA404 1200mg/m<sup>2</sup> + carbo & paclitaxel *versus* carbo + paclitaxel, Q21 days x 6 cycles
- **ATTRACT-2** Second-line, stage IIIb/IV, all histologies,
  - ASA404 1800 mg/m<sup>2</sup> + carbo & paclitaxel

■ ~~Planning Novartis-sponsored studies with other combinations~~  
2Q09

## Breast

- **Phase II, first-line metastatic, HER-2 negative/normal (planned)**
  - ASA404 (1800 mg/m<sup>2</sup>) + paclitaxel vs paclitaxel alone
- **Pilot study with ASA404 +paclitaxel +avastin planned**

## Prostate

- **First-line hormone-refractory**
  - ASA404 1200 mg/m<sup>2</sup> + docetaxel vs docetaxel alone
  - Interim data reported at ASCO 2008; no additional trials planned

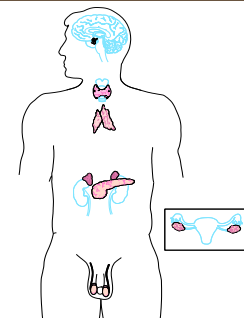
## Ovarian

- **Recurrent platinum sensitive,**
  - ASA404 1200mg/m<sup>2</sup> + carbo & paclitaxel vs carbo + paclitaxel
  - Study completed; RR increased but TTP, OS negative
  - No additional trials planned

# SOM230 – Next-Generation Somatostatin Analogue for Diseases with High Unmet Need

- **Targeted design: 4 out of 5 somatostatin receptors, strong pre-clinical data**
  - SST5-mediated effects in Acromegaly and Cushing's disease
  - SST3-mediated apoptosis pathway
  - Stronger effect on IGF-1 than any other somatostatin analogue
- **Encouraging clinical data**
  - Clinical response in Cushing's disease and refractory carcinoid
  - Promising data in Acromegaly
  - Good safety profile

- 1 Cushing's disease**
  - Wide range of debilitating symptoms



LifeART image © Lippincott, Williams & Wilkins

- 2 Carcinoid Syndrome**
  - Life-threatening complications



- 3 Acromegaly**
  - Significant morbidity and mortality



<sup>1</sup> *Gastroenteropancreatic-neuroendocrine tumors*

# SOM230 Clinical Program

## Carcinoid

- C2303 - Phase III, vs pbo, SOM in Carcinoid (SAS resist/refract)



## Acromegaly

- C2305 - Phase III, SOM in acromegaly



## Cushings

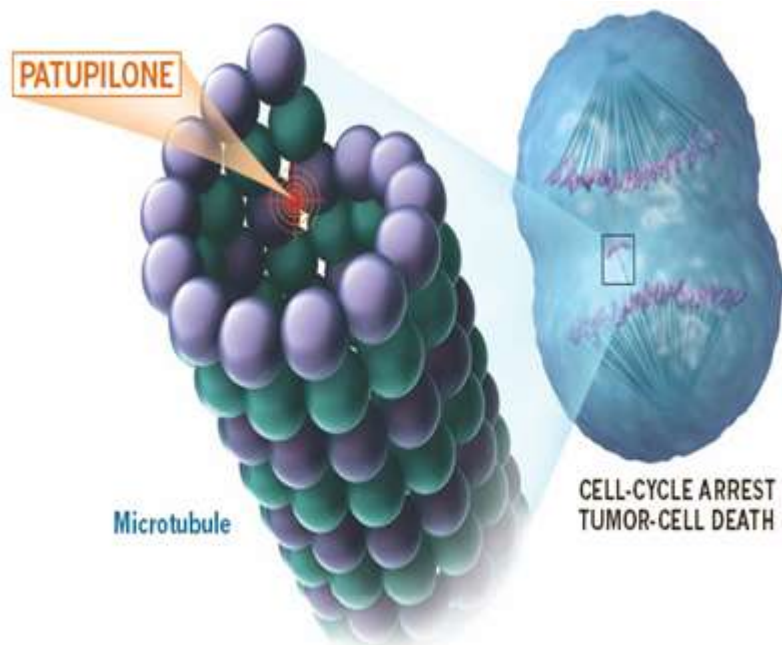
- B2305 - SOM 230 sc Cushing's disease
  - Double-blind randomized study of 2 SOM dose levels over 6 months
- Plan LAR study in 2009



## MBO

- Plan to initiate MBO study in 2009

# EPO906 (patupilone) - Microtubule Stabilizer that Overcomes Tumor Resistance



**Weak substrate for major drug efflux pumps including P-gp**

- EPO 906 (patupilone) is a novel microtubule stabilizer not affected by many common tumor resistance mechanisms
  - Weak substrate for efflux pumps
  - Different  $\beta$ -tubulin binding site than taxanes
  - Increased tumor exposure compared with taxanes
  - Crosses blood-brain barrier in animal models
- Demonstrated clinical efficacy in taxane-resistant and sensitive tumors (ovarian, NSCLC, prostate, breast, CRC, brain mets)
- Predictable and manageable safety profile

Bollag DM et al. *Cancer Res.* 1995;55:2325-2333; Buey RM et al. *Chem Biol.* 2004;11:225-236; Nettles JH et al. *Science.* 2004;305:866-869

# EPO906 (Patupilone) Phase III Study in Recurrent Ovarian Cancer

- Recurrent epithelial ovarian, primary fallopian or primary peritoneal cancer
- Resistant/refractory prior i.v./IP platinum based chemo (up to 3 regimens)
- Failed platinum-based treatment after 4 cycles or relapsed within 6 mo of completion

N=810

Randomization

Patupilone 10 mg/m<sup>2</sup> i.v. q3wk

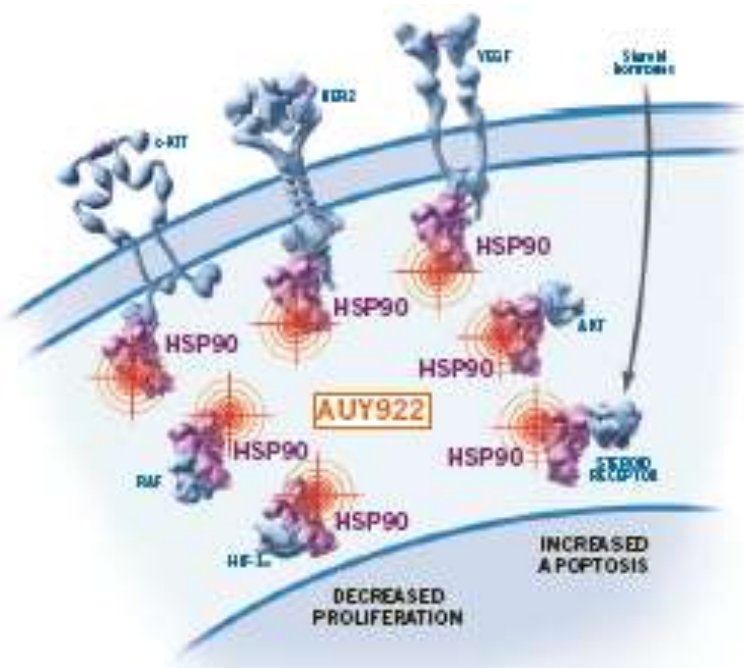
Primary endpoint: OS

Pegylated liposomal doxorubicin 50 mg/m<sup>2</sup> i.v. q4wk

This study is currently enrolling

**Other indications: Expanding development to include HRPC, third/fourth-line CRC, GBM**

# AUY922: Potent Hsp90 Inhibitor

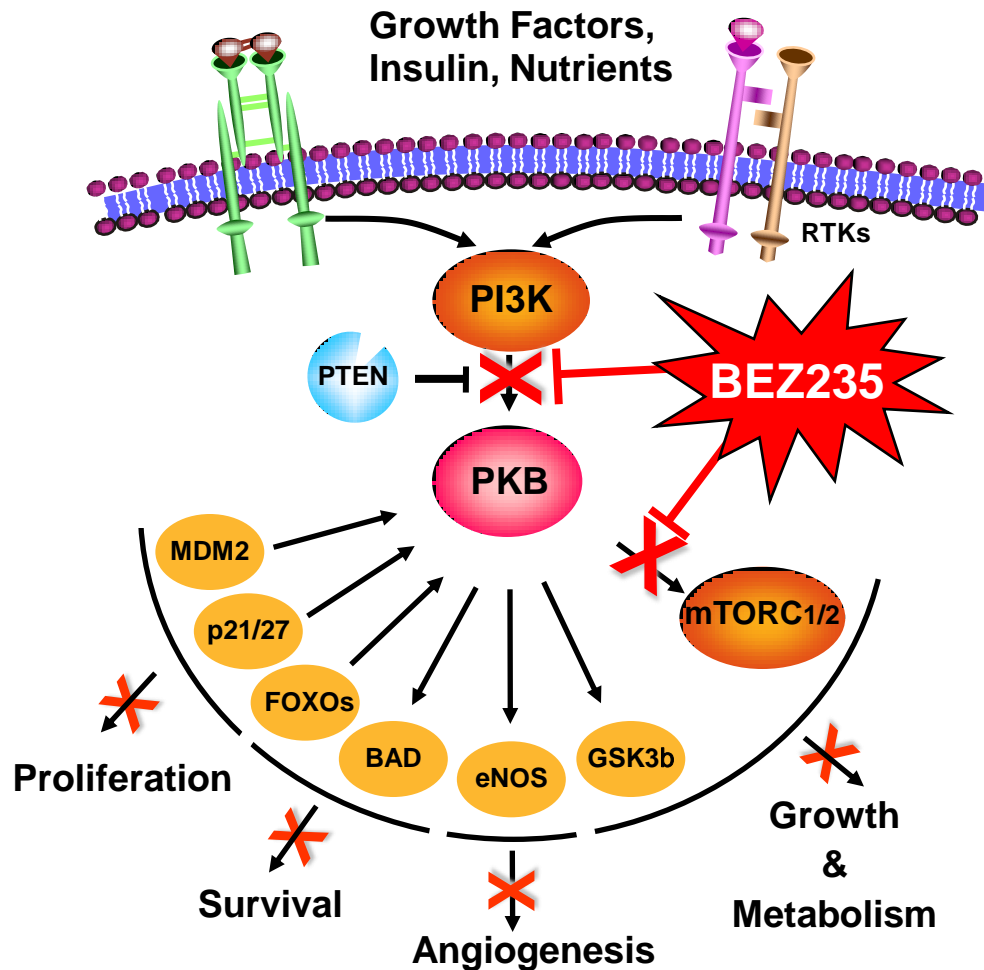


- Hsp90 inhibition and multiple pathway suppression
- Demonstrated broad anti-proliferative activity in a wide variety of tumor types
- Preclinical activity in human breast cancer cell lines (HER2+, HER2-, ER+, ER-)
- Anti-tumor effects in breast cancer xenograft models

**AUY922  
clinical  
program**

- In Phase I/II testing in patients with advanced solid tumors
- Plans for evaluation in breast cancer (Her2+, initiate 2009), gastric cancer (initiate 2009) pancreatic cancer, MM, and other tumors

# PI3K Inhibition and Cancer Suppression



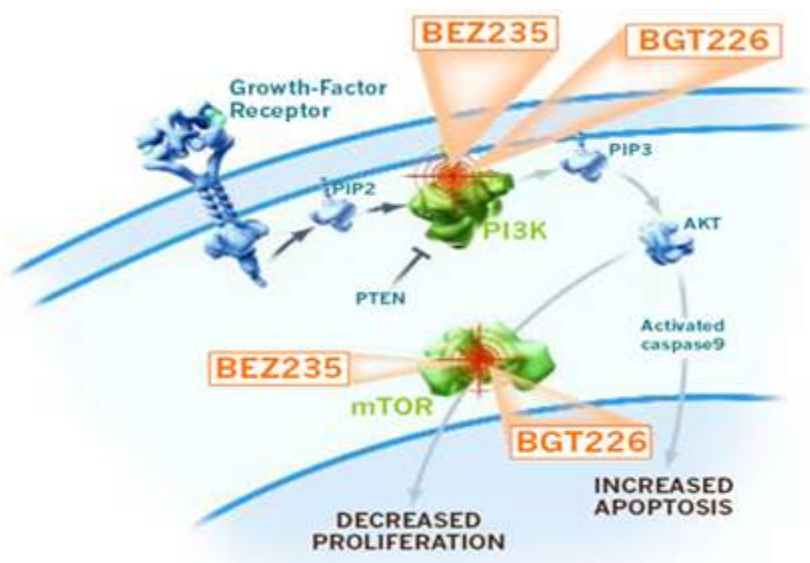
- PI3K is mutated (activated) in many cancers
- Genetic mutations leading to PI3K pathway activation are very common in human malignancies
- Loss-of-function mutations affecting negative regulators of PI3K, such as PTEN
- Gain-of-function mutations affecting activators of PI3K

<sup>1</sup> Phosphoinositide-3 kinase

# BEZ235/BGT226 1st Dual Targeted PI3K/mTOR Inhibitors in Clinical Trials

ASH2008: Poster presentation - "Effective targeting of the PI3-K pathway in CLL with NVP-BEZ235, a novel orally available dual PI3K/mTOR inhibitor"

December 8<sup>th</sup>, 5:30-7:30p

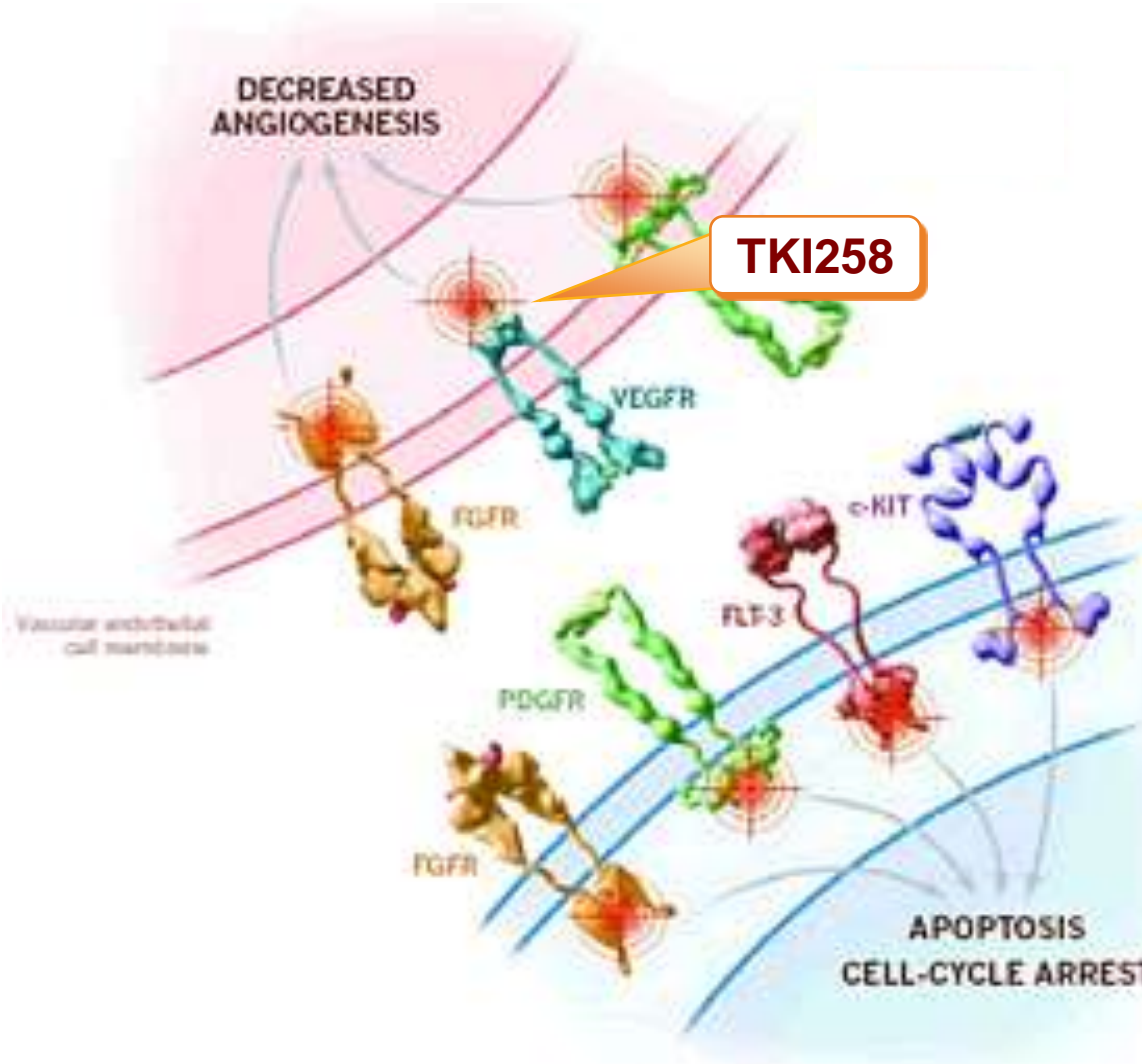


- BEZ235 and BGT226 are oral, potent pan-class I PI3K and mTOR complex 1/2 inhibitors
- Low nanomolar concentrations of either agent inhibit both non-mutant and mutant forms of PI3K
- Dual inhibition of the PI3K pathway with BEZ235/BGT226 may be more effective at controlling tumor growth

**BEZ235/BGT226  
clinical program**

- BEZ235: In Phase I studies in solid tumors, enriched for patients with breast cancer
- BGT226: Phase I studies in solid tumors
- Plans to evaluate compounds in breast (focusing on PI3K and PTEN mutations), NSCLC, GBM, prostate and CRC

# TKI258 - Small-Molecule Inhibitor of Multiple Receptor Tyrosine Kinases, Including FGFR



- TKI258 is a potent inhibitor of multiple kinases
- Potential for dual anti-tumor and anti-angiogenic activity
- Induces apoptosis in preclinical models of various cancers
  - AML, MM, prostate, breast, colon, lung, and ovarian
- Clinical plan focuses on mBC with FGFR mutations, bladder cancer, multiple myeloma)

# TKI258 – Small-Molecule Inhibitor of Multiple Receptor Tyrosine Kinases, Including FGFR

Compound	PDGFR	VEGFR	FGFR	FLT3	EGFR
TKI258	✓	✓	✓	✓	✓
Sunitinib	✓	✓		✓	✓
Sorafenib	✓	✓		✓	✓
AMG706	✓	✓			✓
PKC412		✓		✓	

**TKI258  
clinical  
program**

- Ongoing Phase I studies in multiple tumors, including melanoma, AML, RCC, and multiple myeloma
- Plans to initiate studies in bladder cancer, MBC, and HCC

# RAF265 – Under Study in Melanoma

## Melanoma and B-Raf

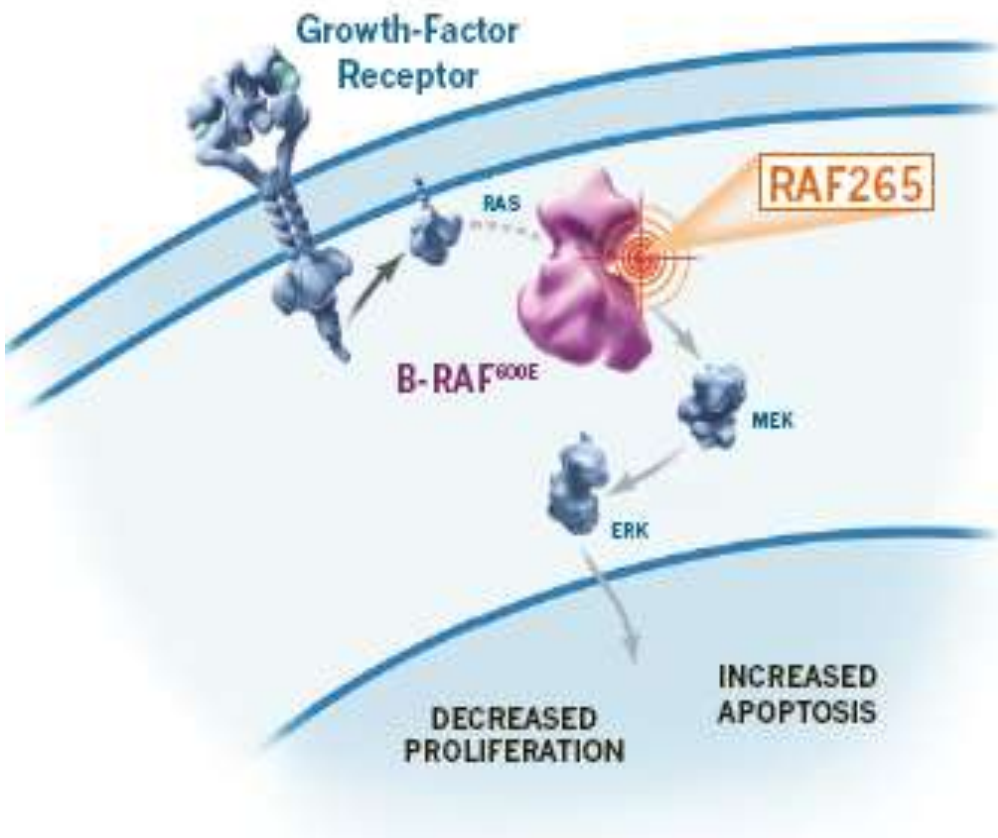


- Melanoma responsible for 8000 deaths/yr in US alone
- Substantial unmet need for better therapies
- Activating mutations in B-Raf gene have been observed in melanoma as well as other tumors

**RAF265  
Clinical  
program**

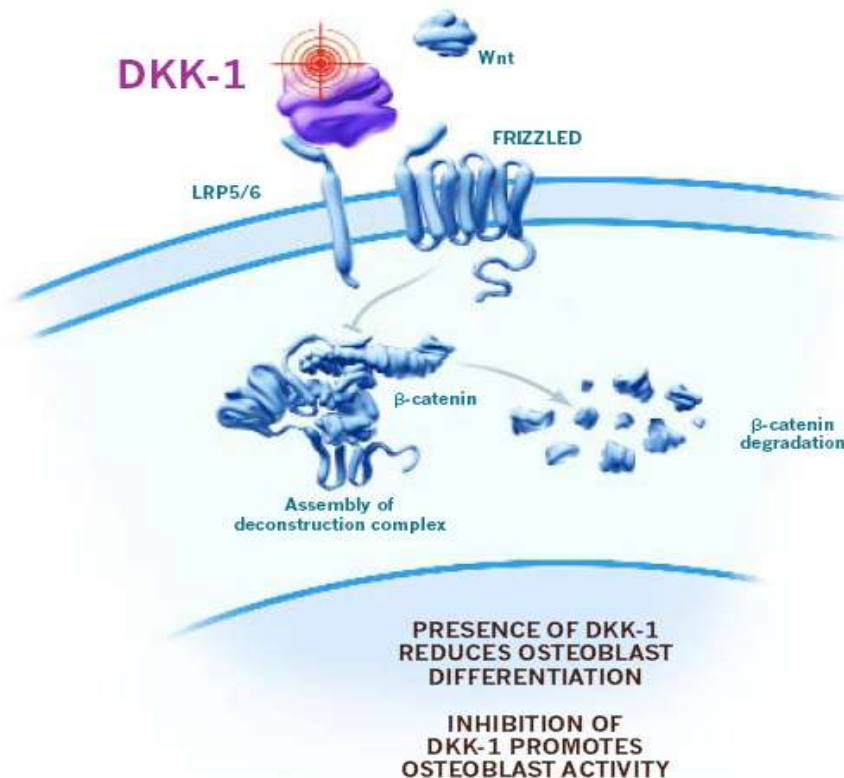
- Ongoing Phase I open-label dose escalation study underway in patients with locally advanced or metastatic melanoma
- Exploratory studies in b-RAF and k-RAS mutant CRC being planned

# RAF265 – Small-Molecule Inhibitor of Mutant B-Raf and VEGFR Kinases



- **RAF265 is highly selective and potent inhibitor of all 3 isoforms of raf kinases**
- **RAF265 demonstrates potent anti-tumor activity in preclinical models of mutant B-Raf**
- **RAF265 also has anti-angiogenic activity through inhibition of VEGFR-2**

# BHQ880: First-in-Class, Fully Human, Anti-DKK-1 Monoclonal Antibody



- **BHQ880 neutralizes DKK1 suppression of the Wnt signaling pathway**
- **Wnt pathway activation leads to increase osteoblastic cells**
- **Increased bone mineral density in normal mice and cyno monkeys**

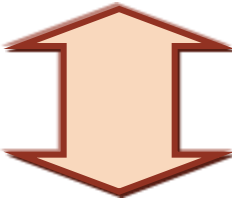
**BHQ880  
clinical  
program**

- **Phase I study in healthy, post-menopausal women**
- **Phase I study relapsed/refractory multiple myeloma with prior SRE planned (with Zometa)**

# Drug Discovery and Innovation: The Core Dilemma

## A. PHARMA INDUSTRY

- 1. Higher R&D Costs
- 2. Smaller Return on Investments
- 3. Falling R&D Productivity



Discover, develop and make accessible effective therapies for cancer !

## B. HEALTH AUTHORITIES

- 1. Increasing/ Higher costs of drugs
- 2. Higher epidemiology in many cancer types



## C. PHYSICIANS

- 1. Need for more effective use of treatments
- 2. Need of high caliber Scientific Projects



## D. PATIENTS (ASSOCIATIONS)

- 1. High need of effective and safe treatments available in the market



**They all have a common goal !**

# Closer collaboration with Oncologists

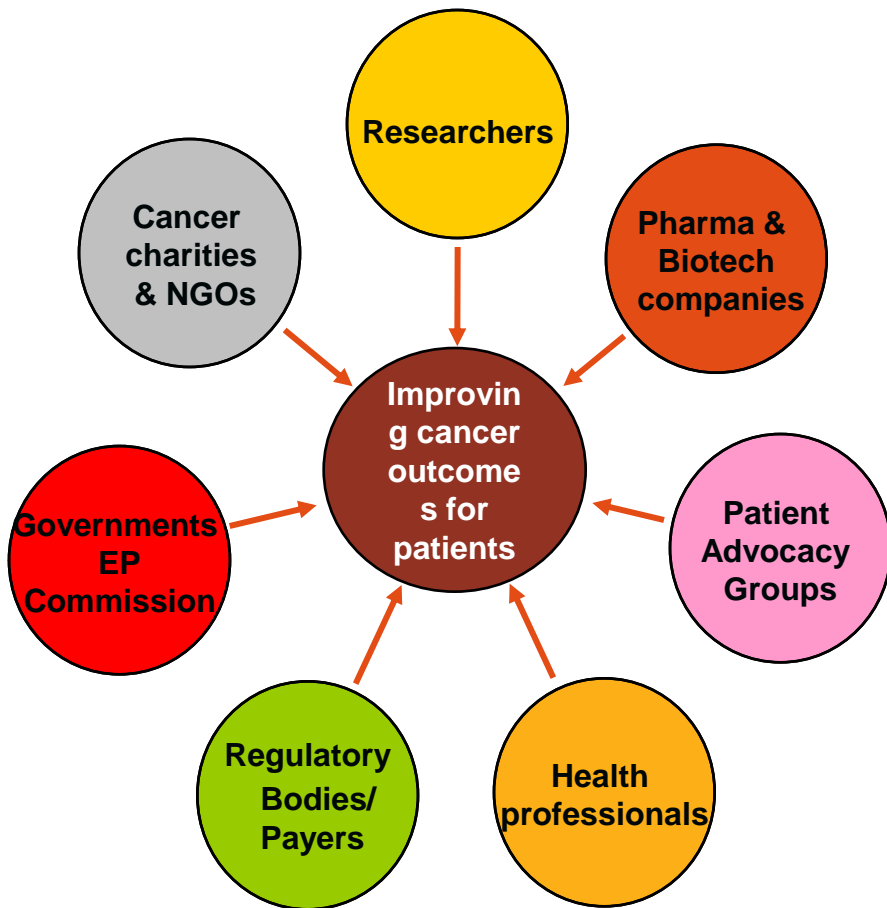
## PHARMA INDUSTRY

- ❑ **Involve more physicians/ patients in clinical trial design**
- ❑ **Support/ cooperate in the development of Networks/ Registries**
- ❑ **Enhance transparency in clinical trials/ data**
- ❑ **Enhance services offering/ level**

## ONCOLOGISTS

- ❑ **To create wider and **European/ Local networks of best practices and scientific collaboration****
- ❑ **To create and adopt wider **patients registries to better understand treatment and diseases****
- ❑ **To facilitate and encourage **job rotations of physicians/ scientists between academy and industry worlds****
- ❑ **To embrace a **continued medical education approach** (including clinical trial management), leveraging BLT and molecular monitoring**

# Conclusions - II: Partnerships – Working Together to develop more effective anti cancer drugs



- **Medicines** are one of the key cornerstones in the multimodality treatment of cancer
- **Targeted therapies** represent a major step towards more effective cancer care in the future
- **The fight against cancer relies on commitment from all relevant stakeholders working in partnership with open dialogue**
- **The political/ regulatory framework should work to ensure all cancer patients in Europe have access to the highest attainable standard of cancer care**
- **The whole EU system needs to work more effectively and efficiently. This can only be achieved through **cooperation** among all stakeholder groups**